Working classification of the CDAs 1968

Table IV

Type I:	Megaloblastoid changes, internuclear chromatin bridges, macrocytosis
	5 cases: WENDT und HEIMPEL 1967, HEIMPEL et al. 1967
Type II:	Bi- and multinuclearity, pluripolar mitoses, karyorrhexis, normocytosis
	1 case: SCHÄRER, MARTI and BAUMANN 1965
	2 cases: HEIMPEL and WENDT 1967
	3 cases: VERWILGHEN et al. 1967
	1 case: LEWIS (1967, not published)
Type III:	Multinuclearity with up to 12 nuclei, gigantoblasts, macrocytosis
	4 cases: WOLFF and VON HOFE 1951
	15 cases: BERGSTRÖM and JACOBSSON 1961
	3 cases: DE LOZZIO et al. 1962

Heimpel,H.; Wendt,F. Helv. Acta 1968, 34, 102 -115

CDA I: Two sisters with CDA I

Two sisters with CDA II

CDA_UPN 41501/01:02.JPG

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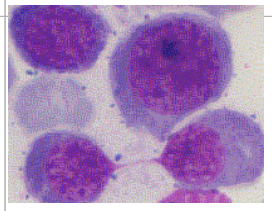
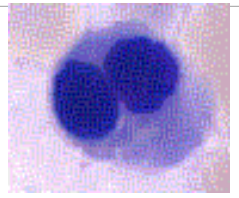
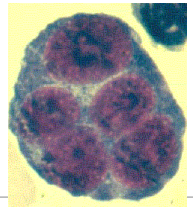
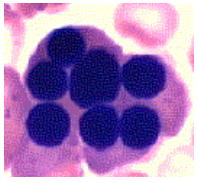
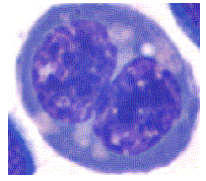
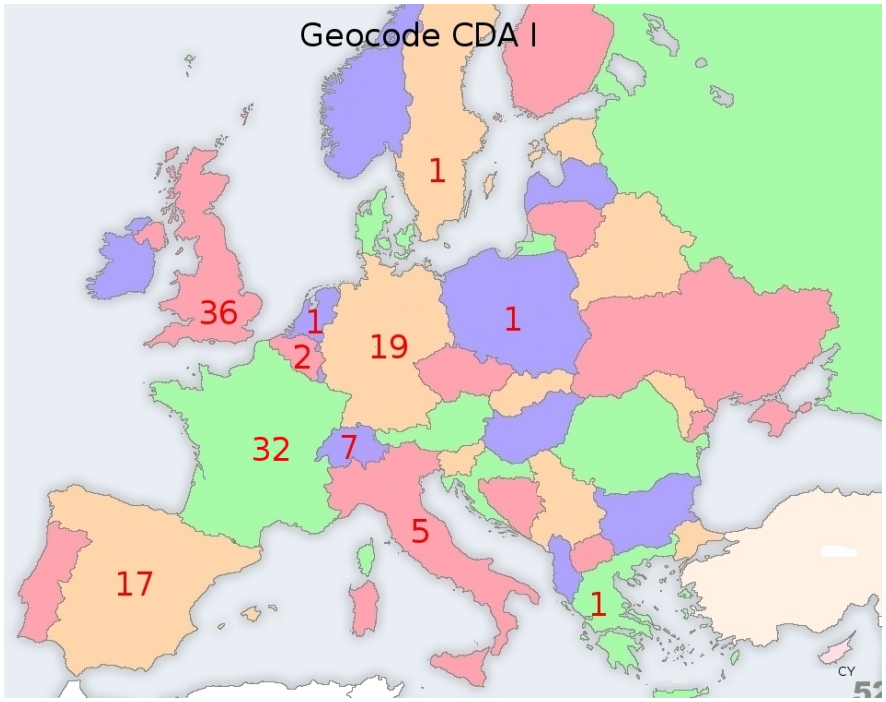
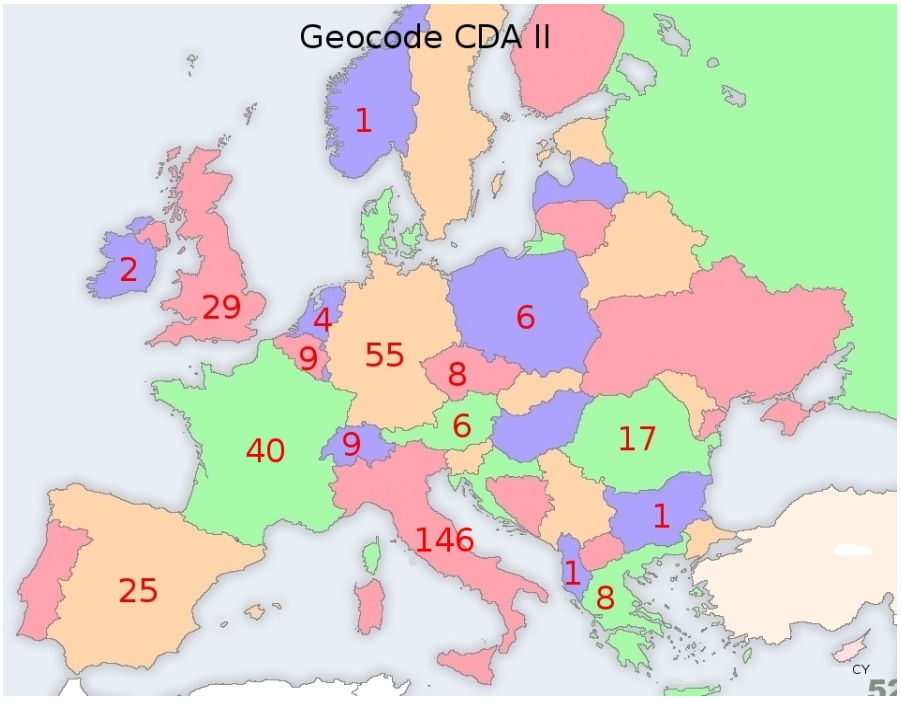
A severe case of CDA II. Boy 495/01, 4 7/12 years

Congenital dyserythropoietic anemias: overview

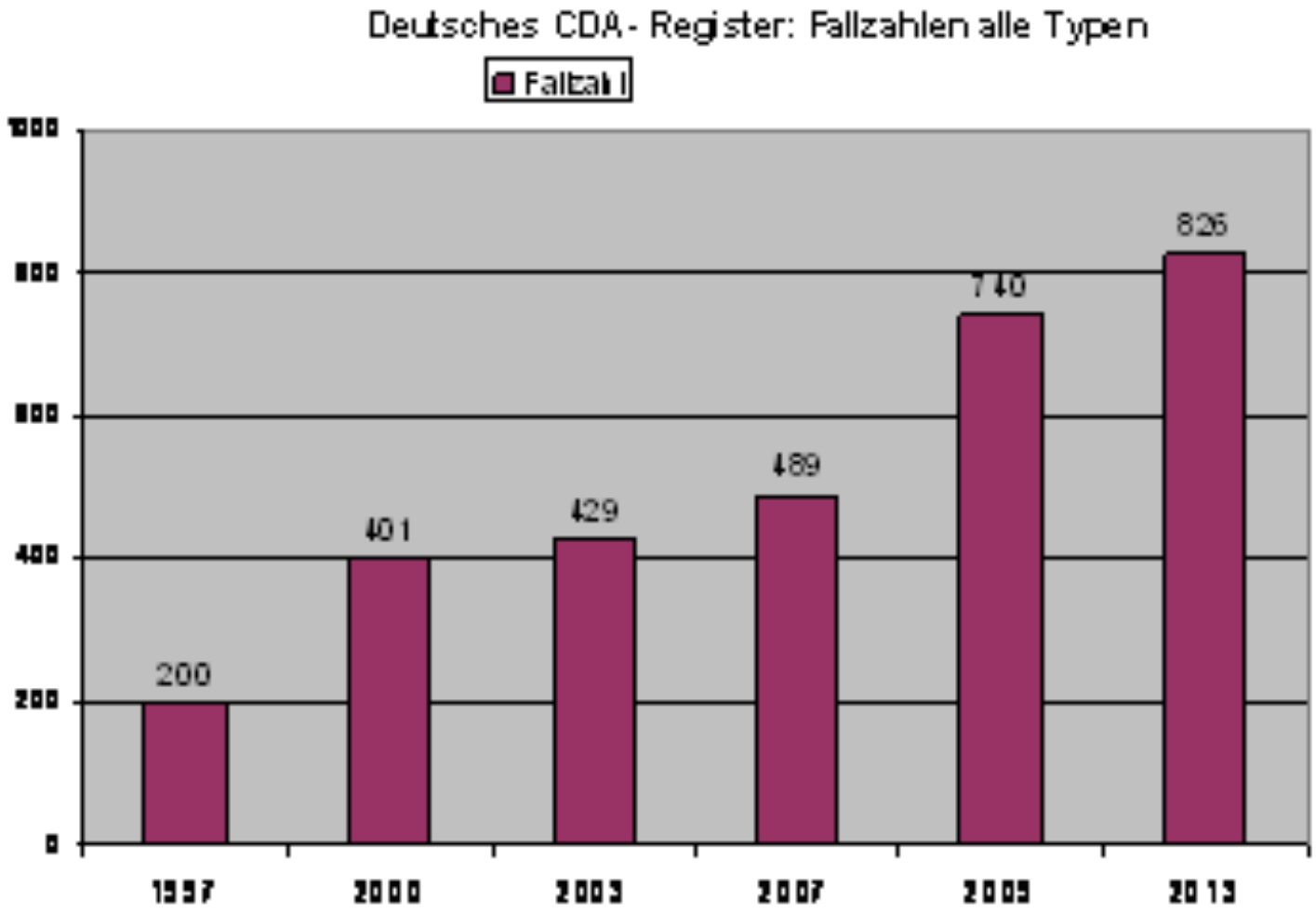
CDA type	I	II HEMPAS	III familial	I I I sporadic	Variants
Inheritance	Autosomal-recessive	Autosomal-recessive	Autosomal-dominant	Variable	Autosomal-recessive or x-linked
Cases reported	~150	> 500	3 families	< 20	~70
Morpho-logy					
Gene Locus	*CDAN1* 15q (15.1.3)	*SEC23B* 20p11.23-20p12.1	*Kif23* 15q (21-25)	Unknown Unknown	Gata1, KLF1, others
Dysmorpho-logies	Skeleton, Others	Variable, rare	B-Cells Retina	Variable	CNS Others

Frequency of CDA I and II in Europe, 2009

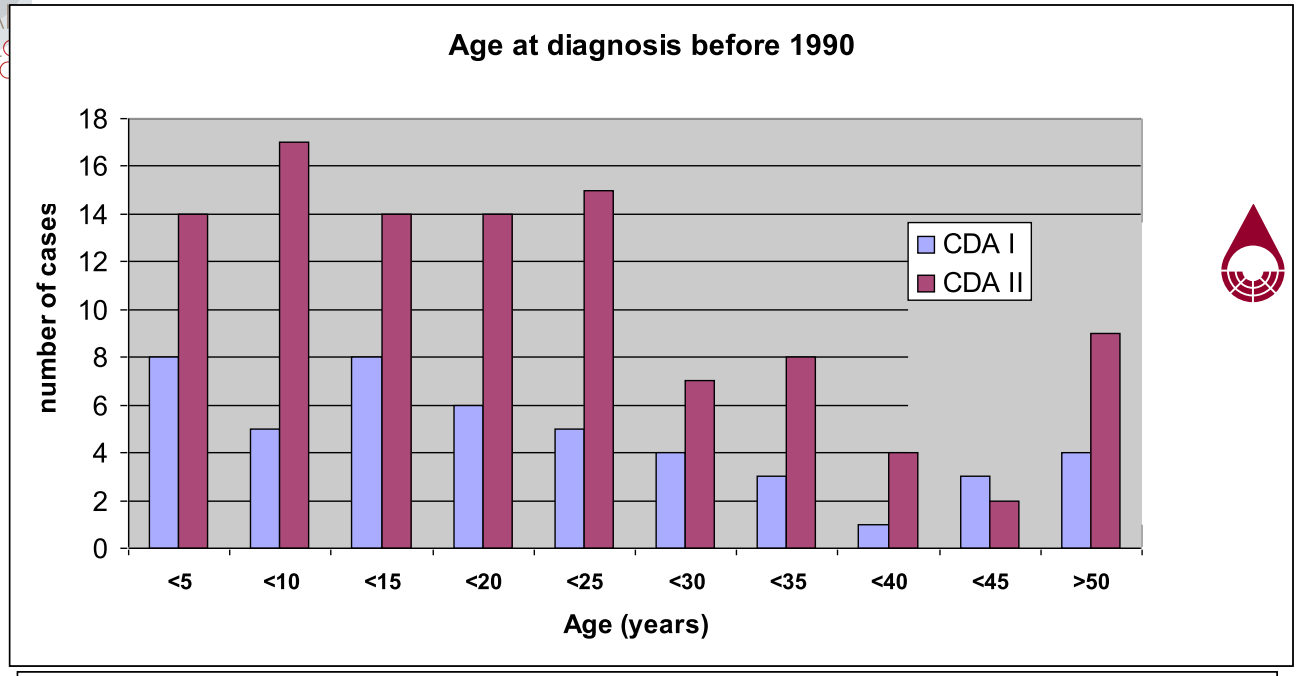


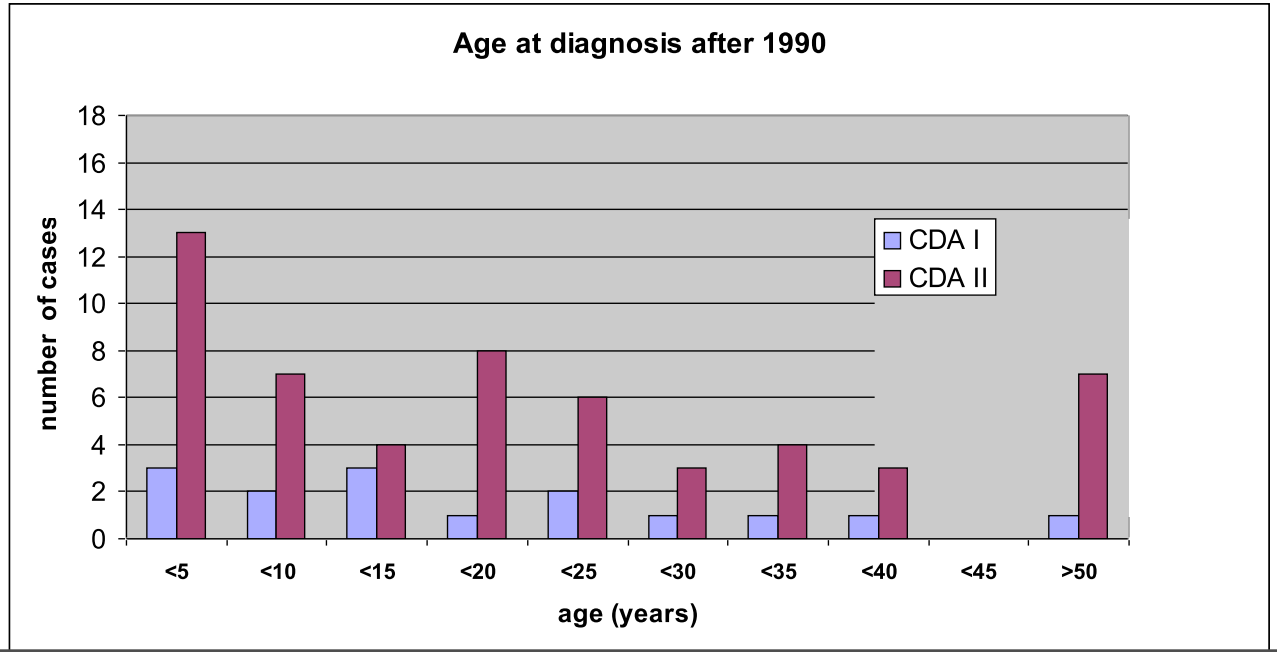


Heimpel et al European Journal of Haematology 2010,85,20-24


Deutsches CDA - Register: Fallzahlen alle Typen
Fallzahl
1000
800
600
400
200
0
200
401
429
489
740
826
1997
2000
2003
2007
2009
2013

Diagnosis of CDAs: Often delayed!





Congenital Dyserythropoietic Anemias (CDAs): Definition

- Evidence of a congenital and/or hereditary disorder
  - history, family studies
- Evidence of ineffective erythropoiesis
  - blood count, bilirubin, haptoglobin, serum transferrin receptor, **reticulocytes inadequate**, bone marrow
- Characteristic morphological abnormalities of erythrocytes and erythroblasts
  - light and electron microscopy
- Exclusion of hemolytic anemias, disorders of hemoglobin synthesis and megaloblastic anemias

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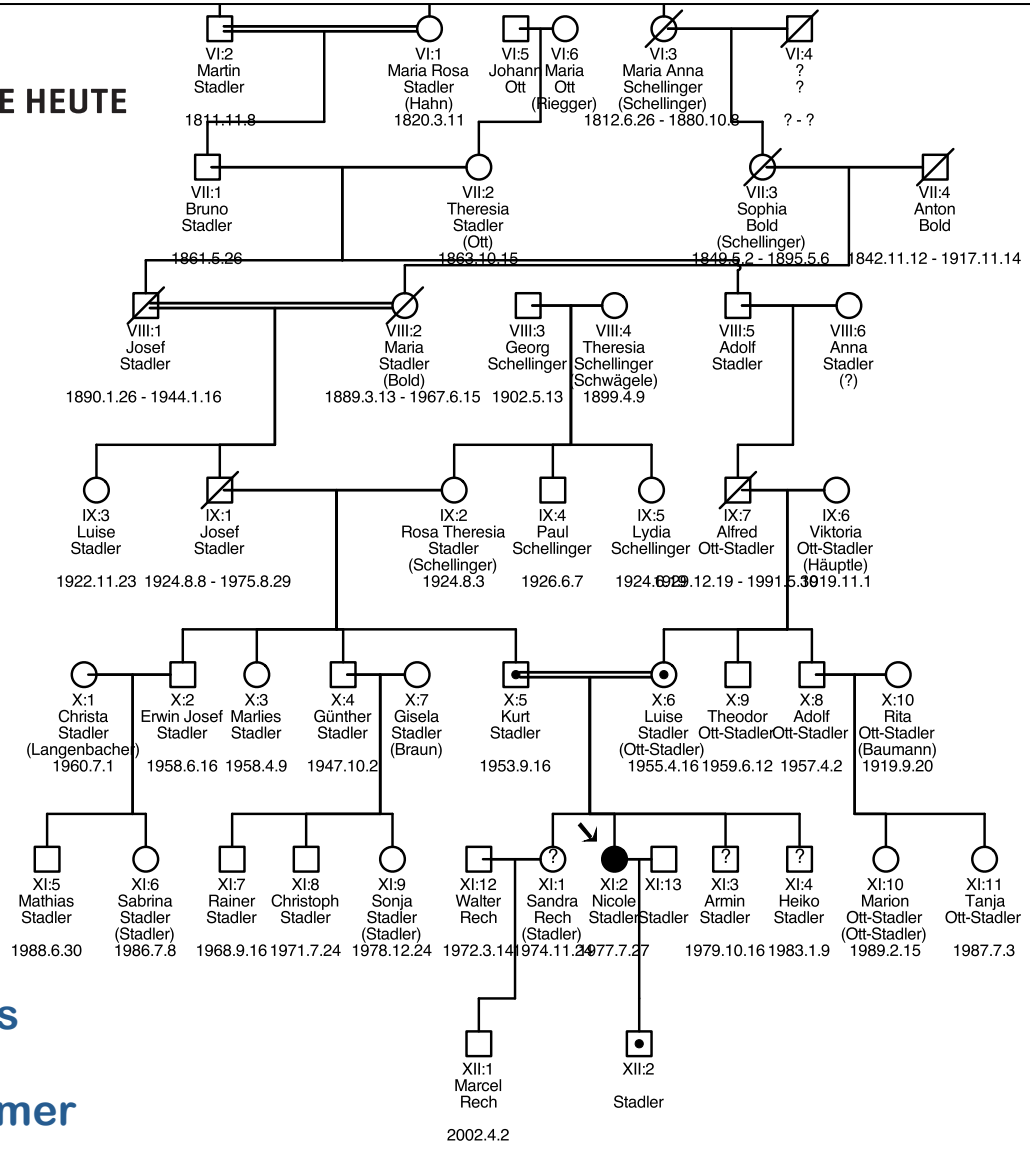
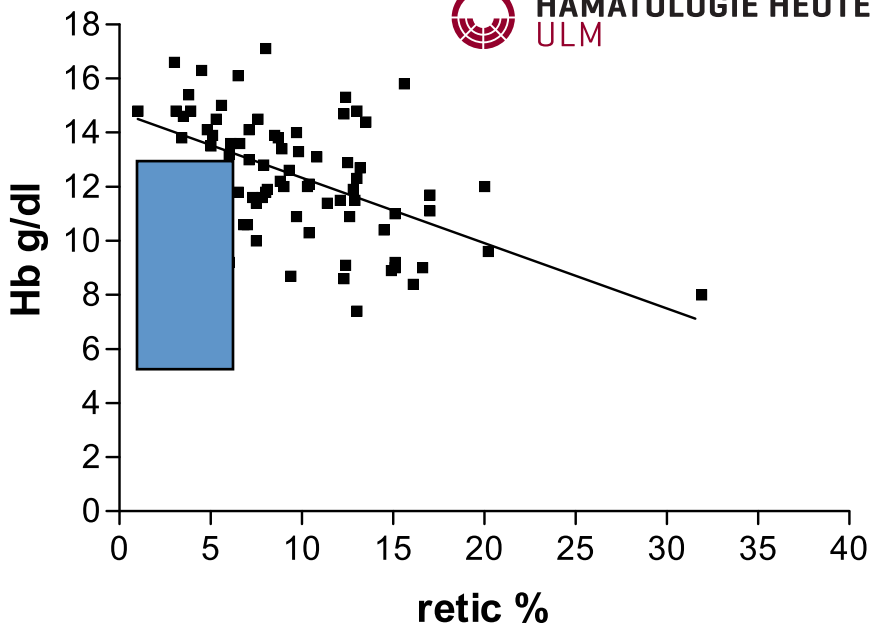
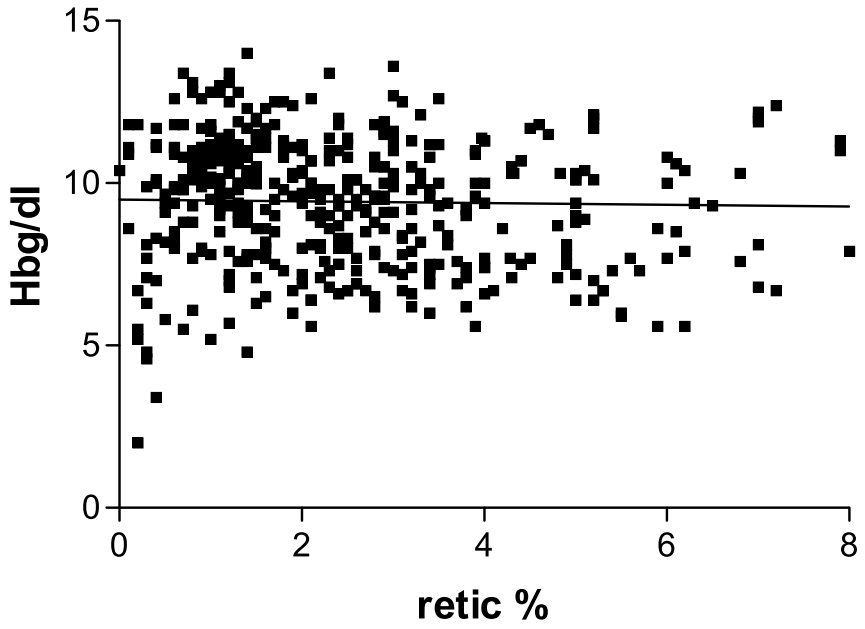
Famile 312



Familie aus Schwaben Gemeinsamer Stamm-Vater gest.1714

Pedigree of the family 412; Stadler; CDA II





Hereditary Spherocytosis

Correlation of hemoglobin and reticulocyte count

Congenital dyserythropoietic anemia type II

Congenital dyserythropoietic anemias: overview

CDA type	I	II HEMPAS	III familial	I I I sporadic	Variants
Inheritance	Autosomal-recessive	Autosomal-recessive	Autosomal-dominant	Variable	Autosomal-recessive or x-linked
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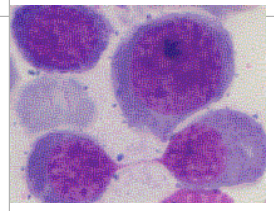
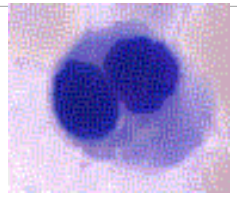
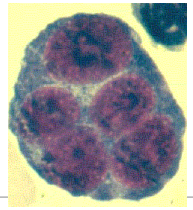
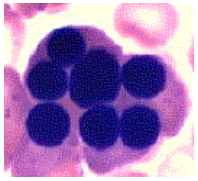
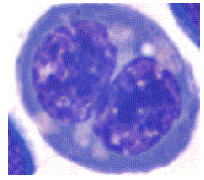
Morpho-logy					
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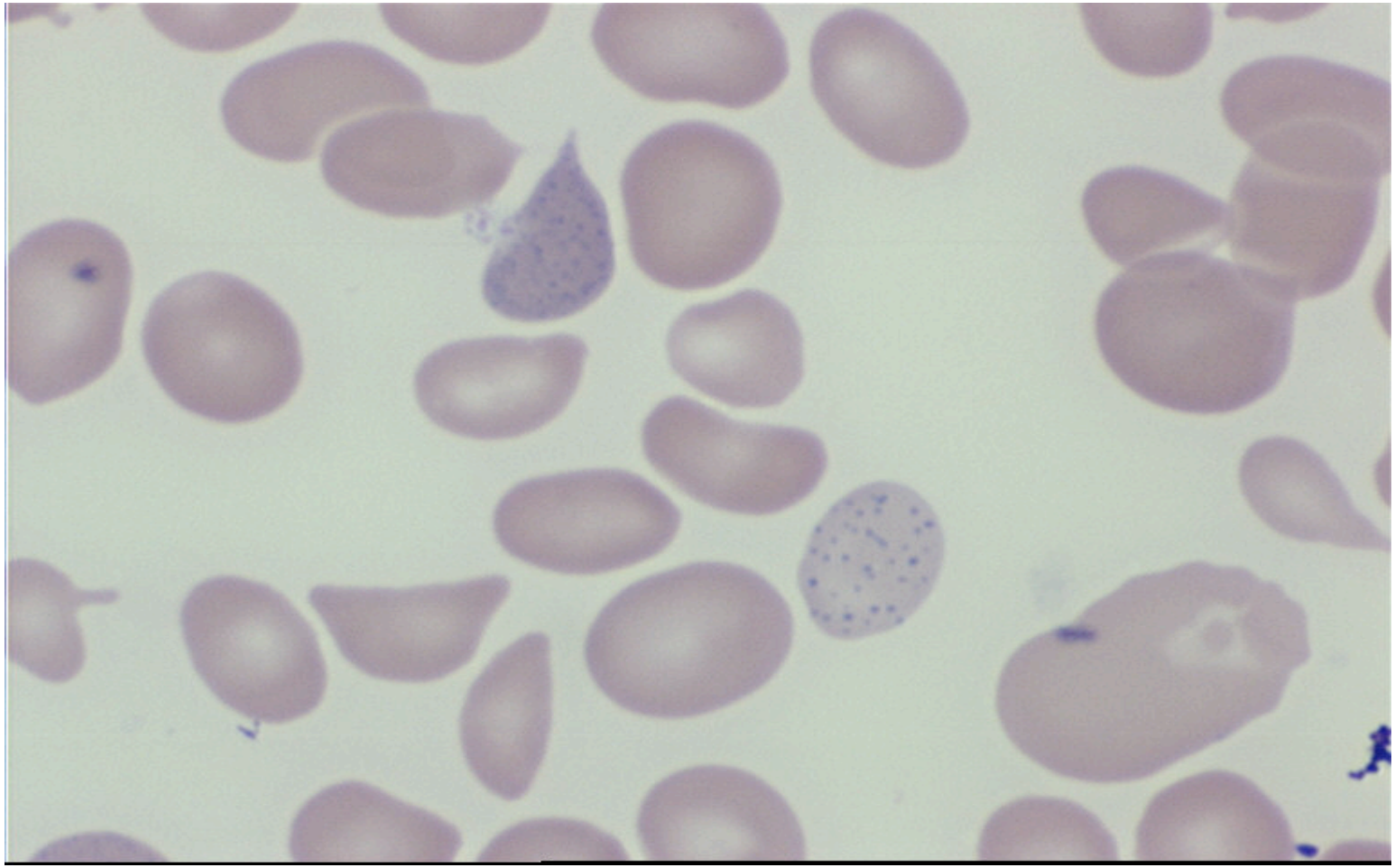
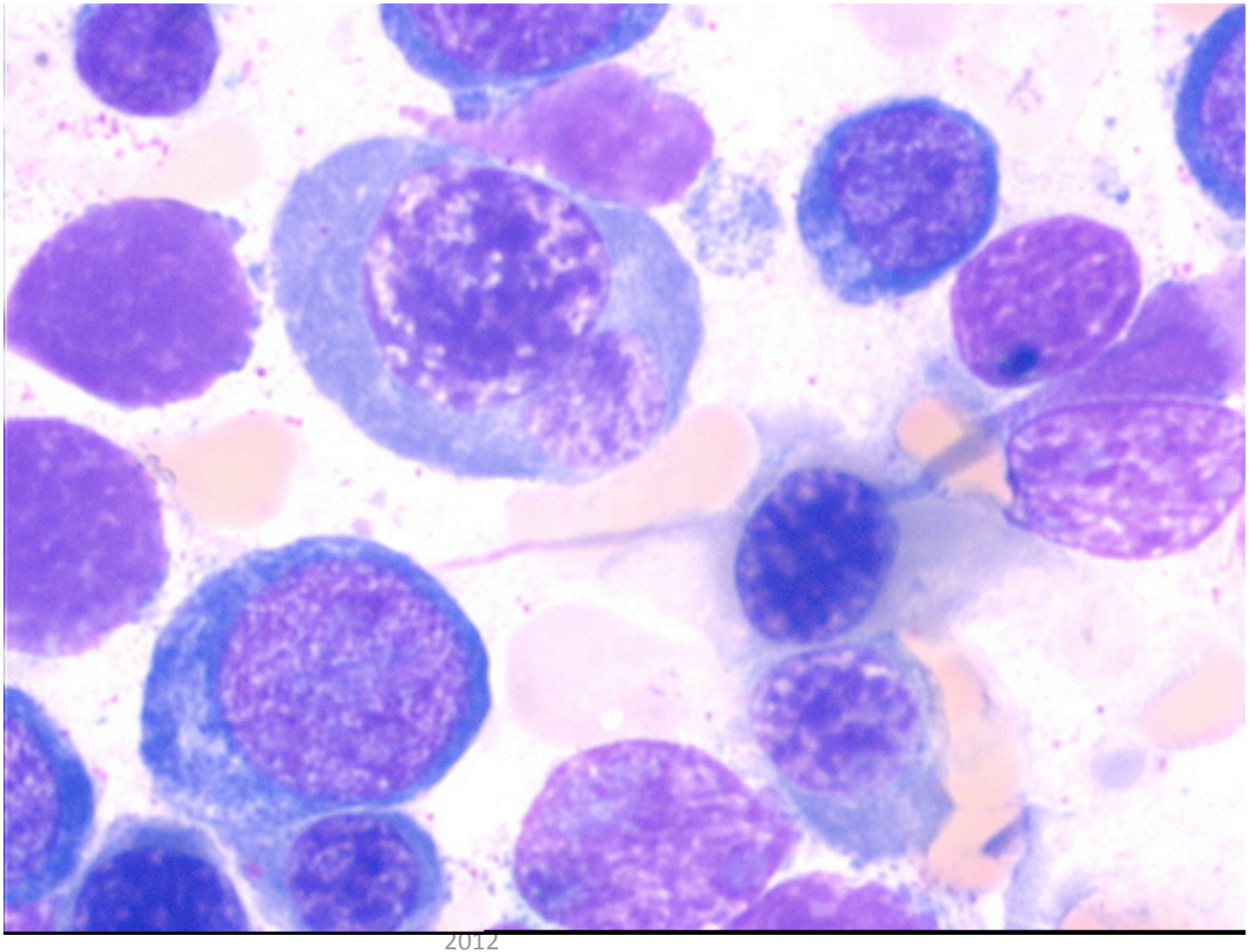
Dysmorpho-logies	Skeleton, Others	Variable, rare	B-Cells Retina	Variable	CNS Others

Grade 3 aniso-poikilozytosis and gross basophilic stippling in a case of CDA I



303/01_20050319_017.jpg

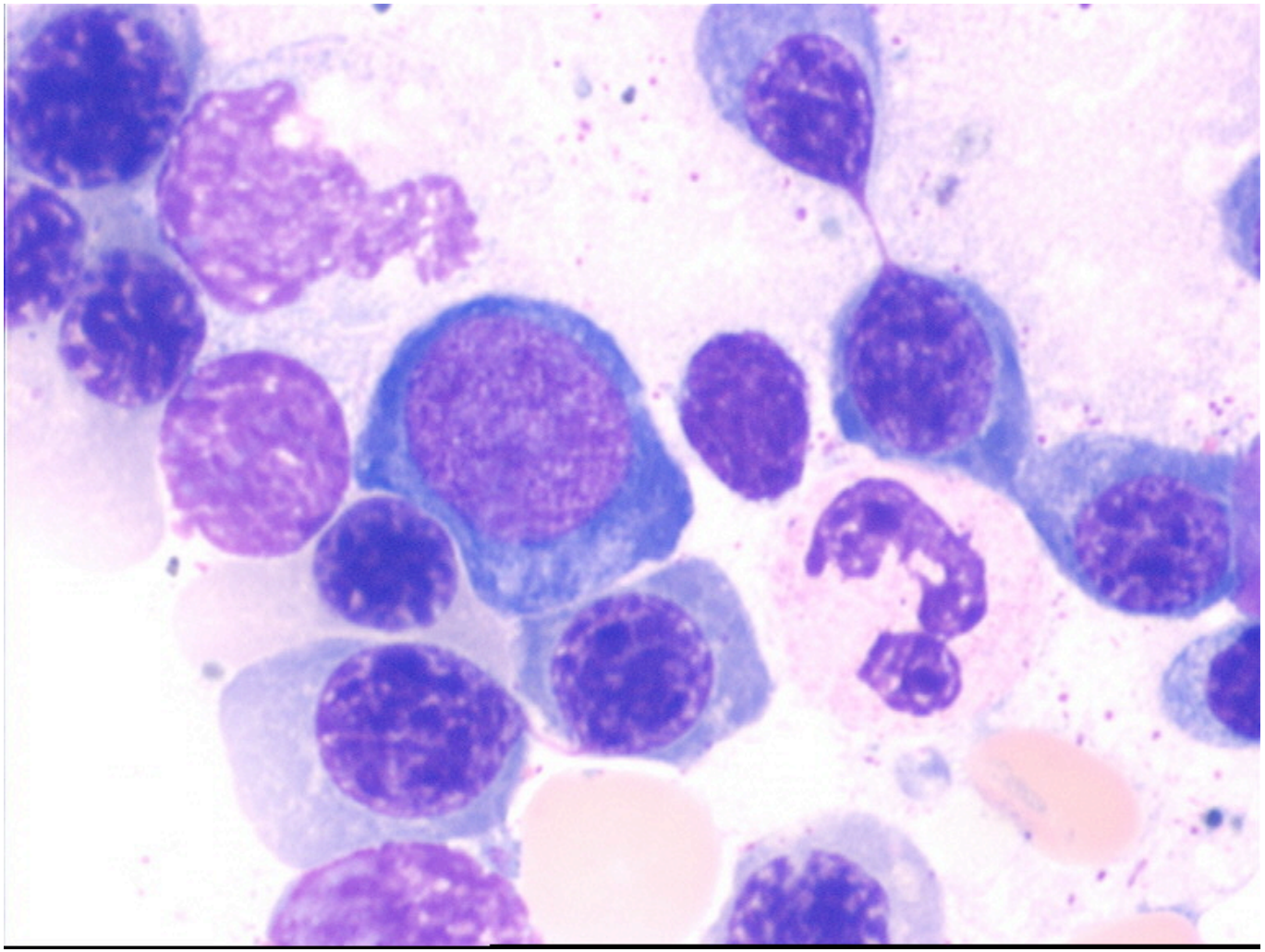
CDAI, KM-Aspirate



2012

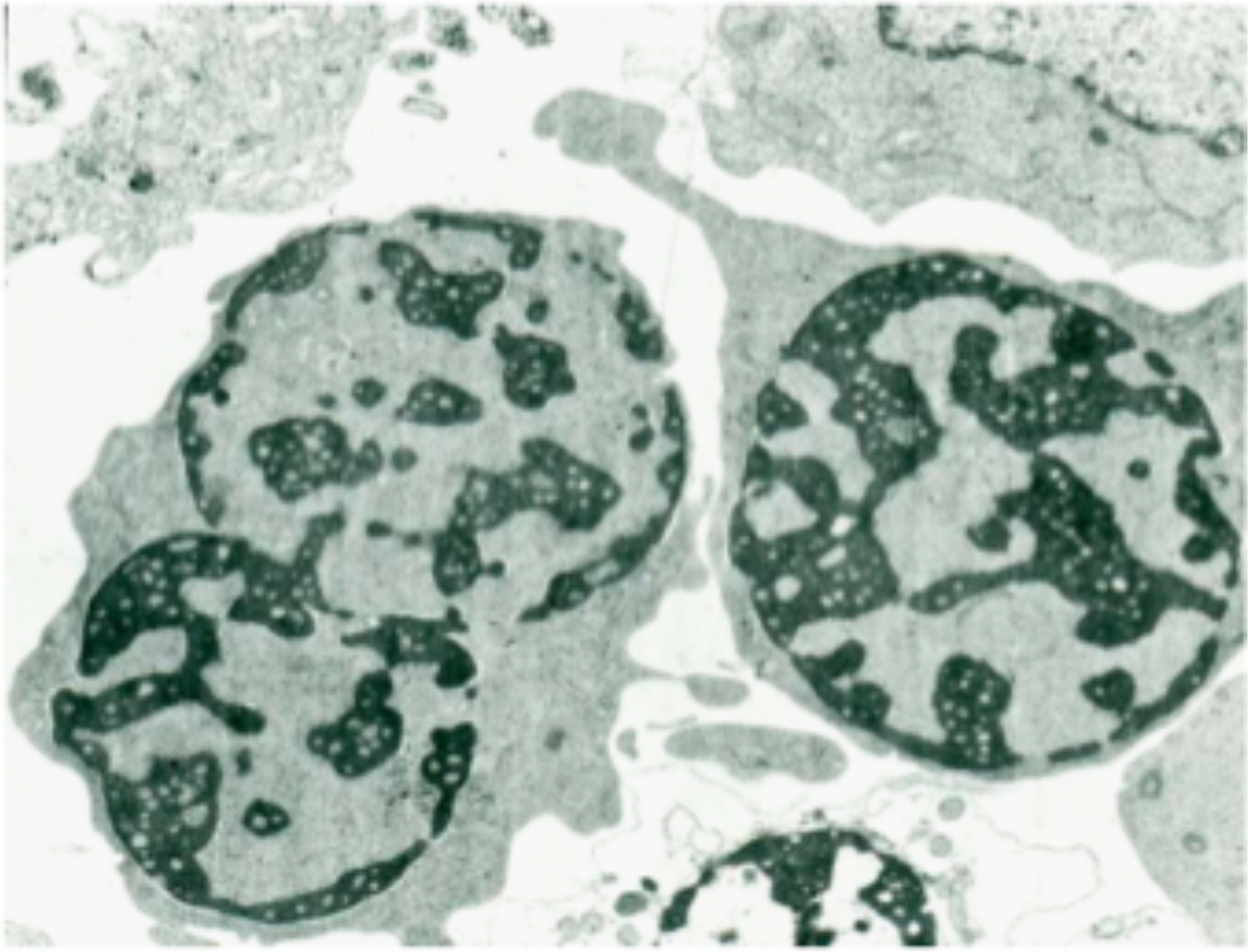
406/01_km_005.jpg

CDA I, KM-Aspirate



406/01_km_006.jpg

Elektronenmikroskopische Aufnahme von Erythroblasten bei CDA I



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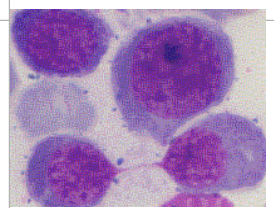
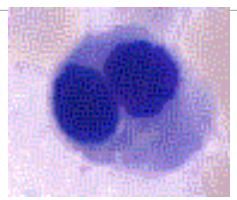
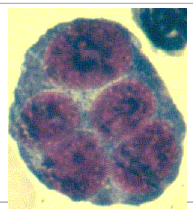
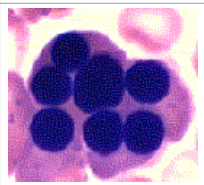
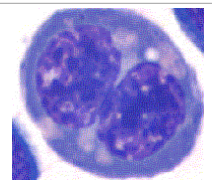
Morpho-logy					
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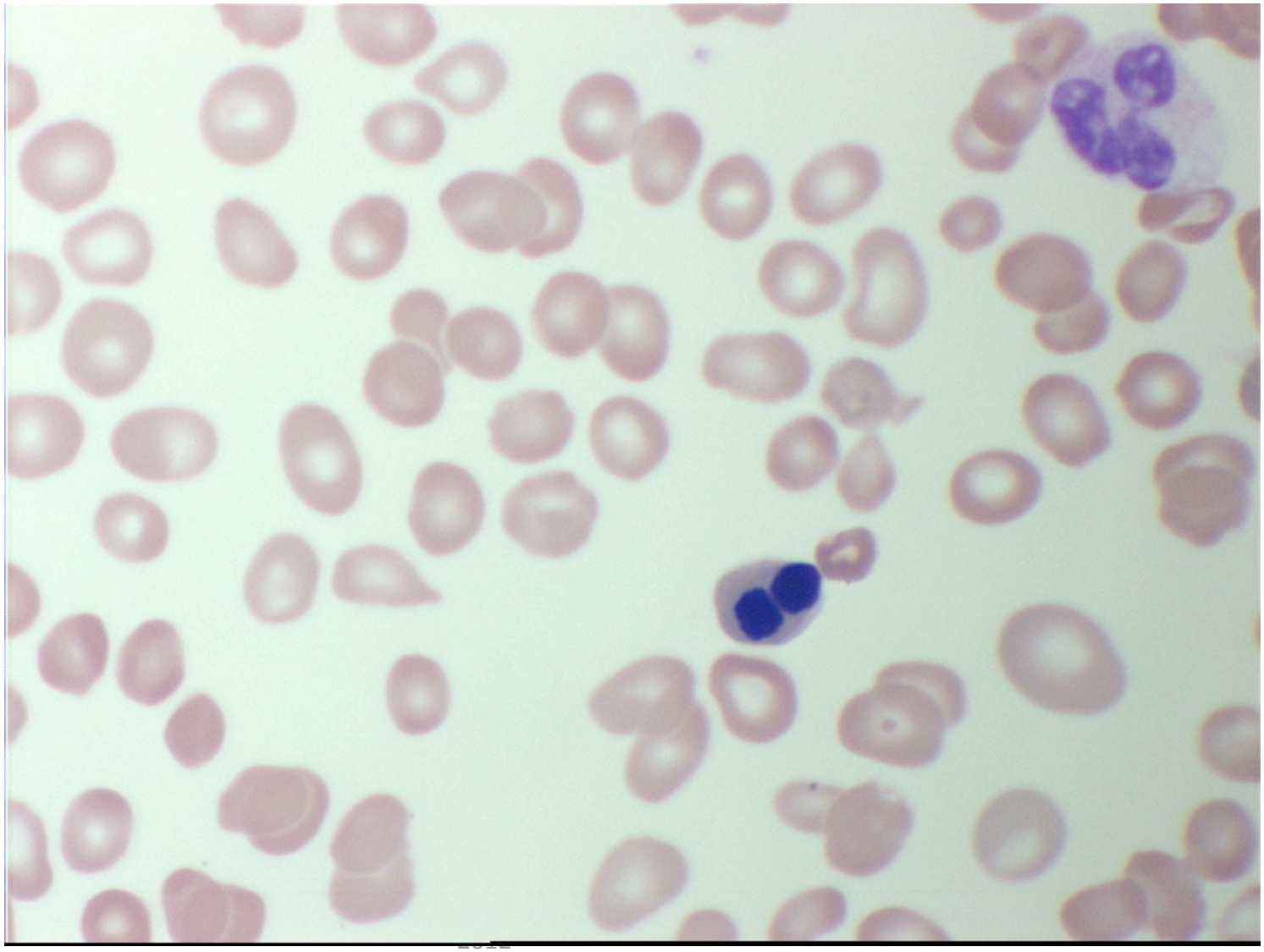
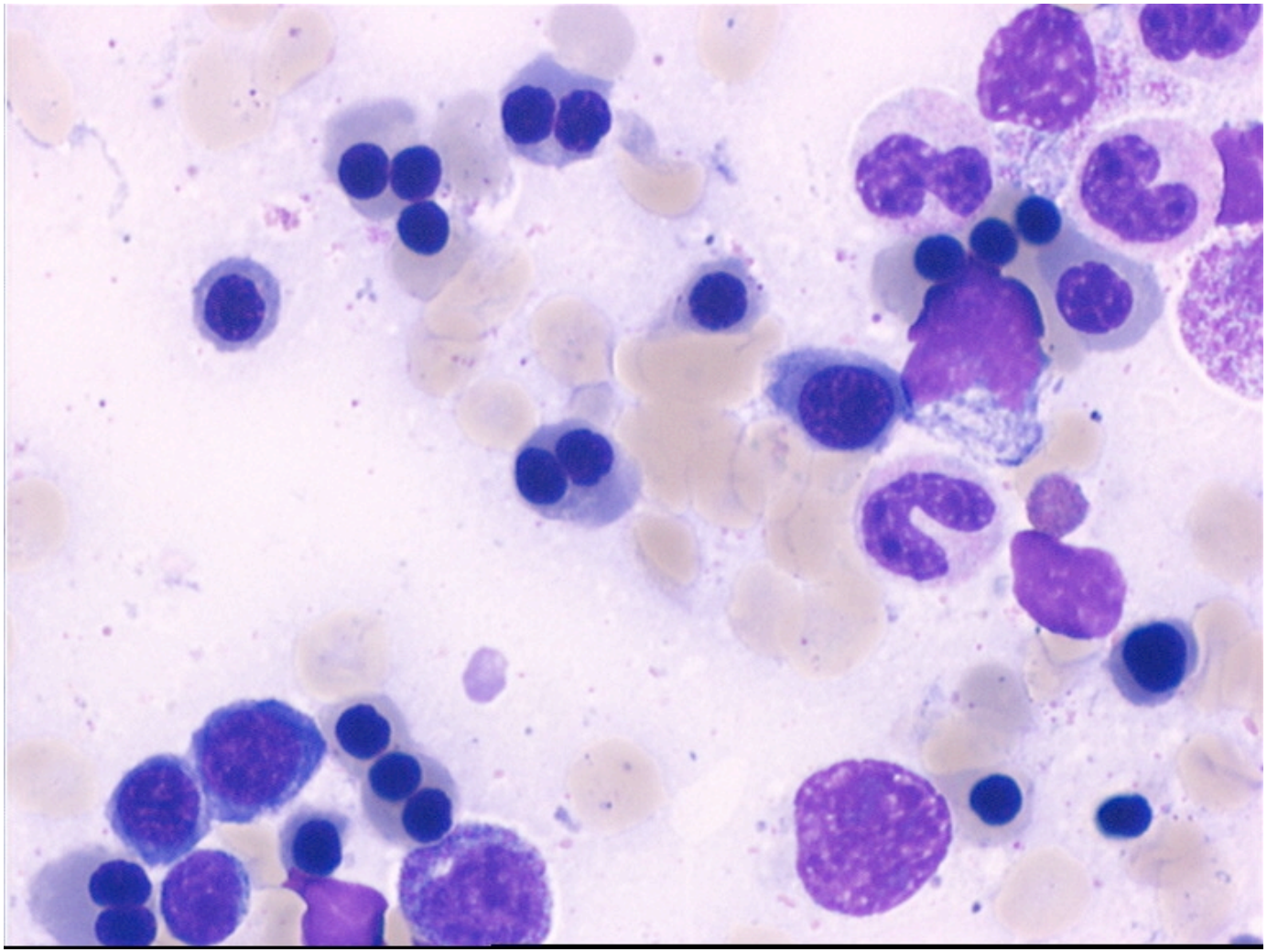
Dysmorpho-logies	Skeleton, Others	Variable, rare	B-Cells Retina	Variable	CNS Others

CDA II: Anisopoikilocytosis, binucleated erythroblast



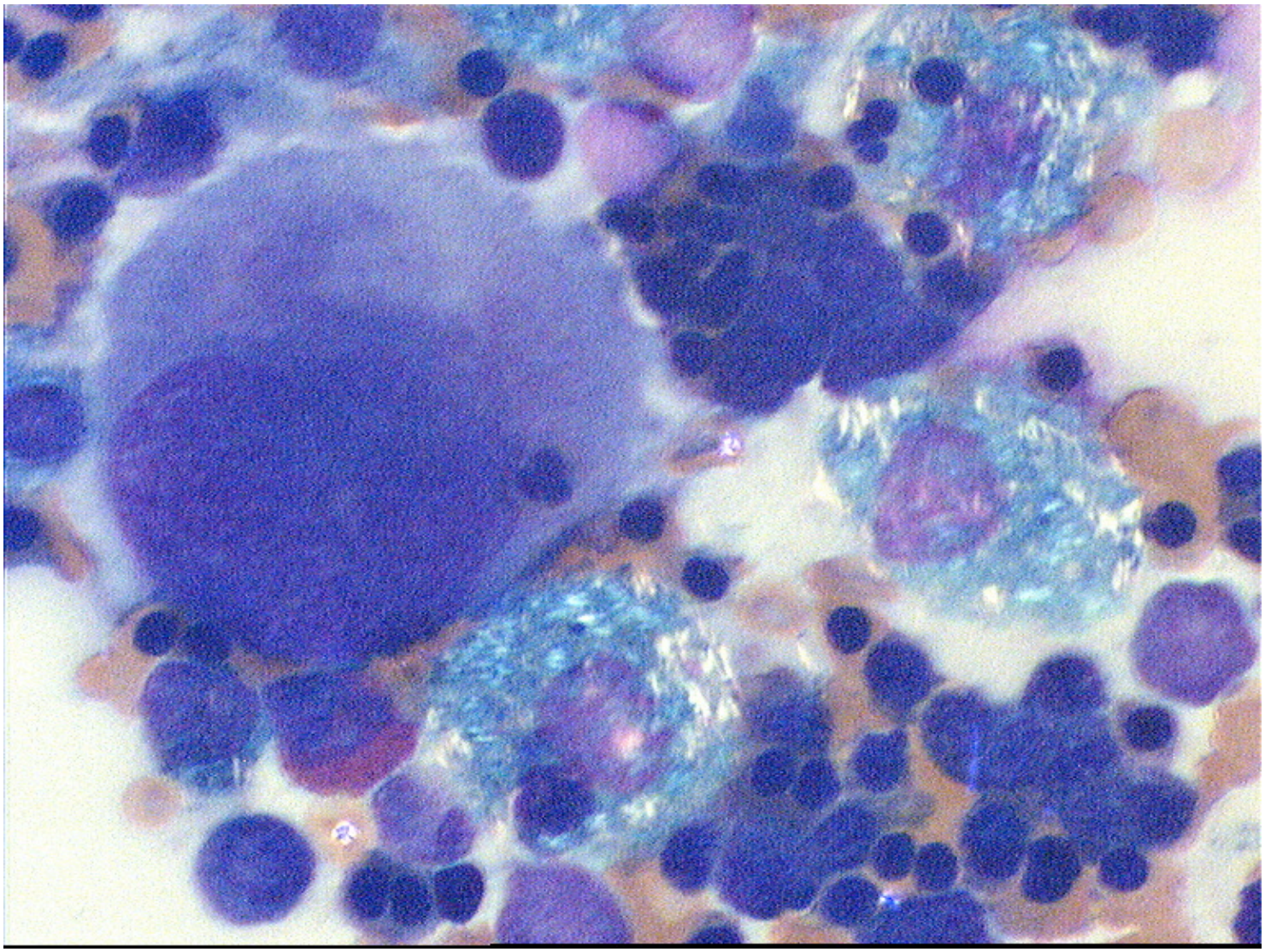
415/02__000001.jpg

CDA II: Nuclei of binucleated normoblasts have identical shape and DNA-content



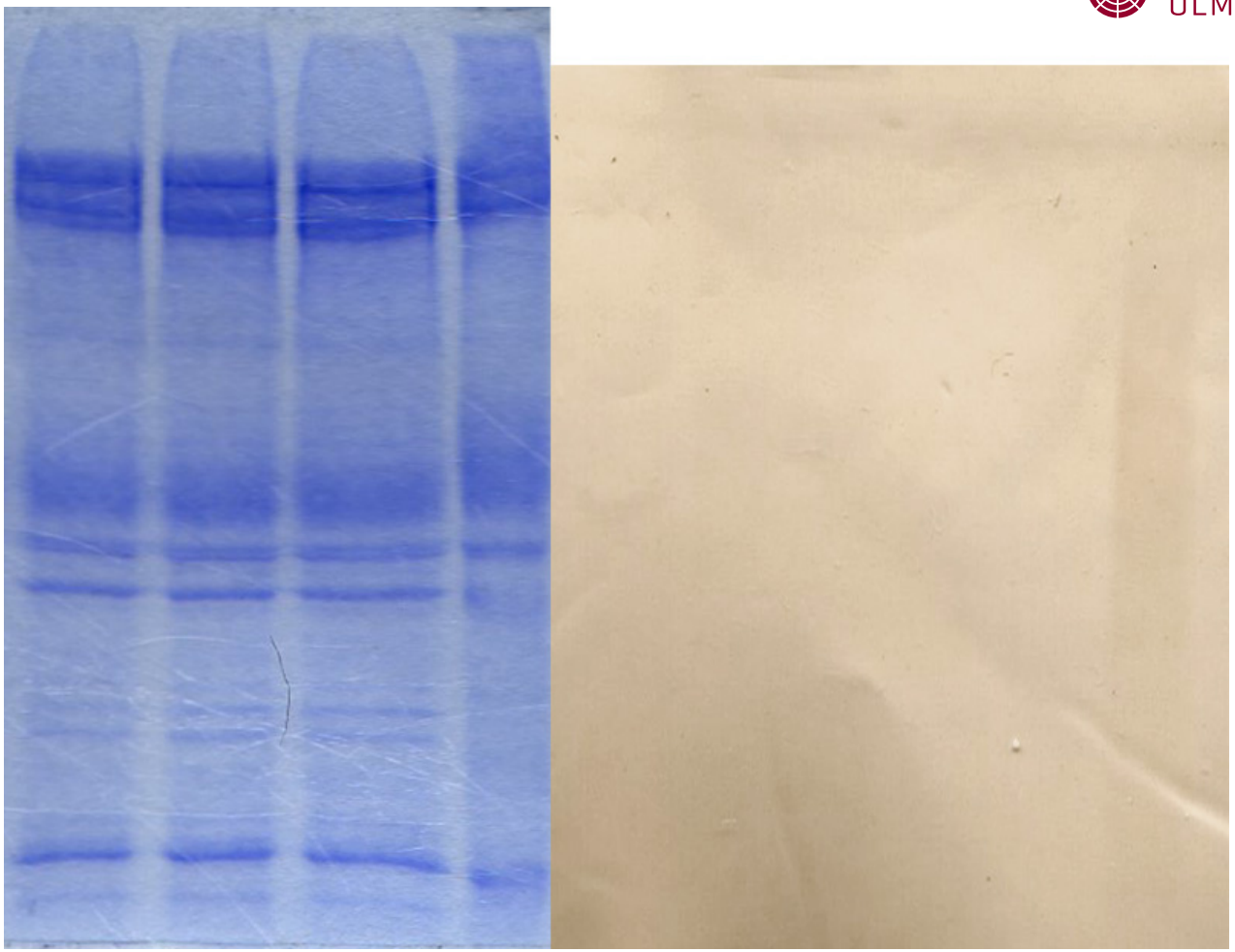
UPN_ 478/01

CDA II: Pseudo-Gaucher-cells containing birefringent membrane remnants

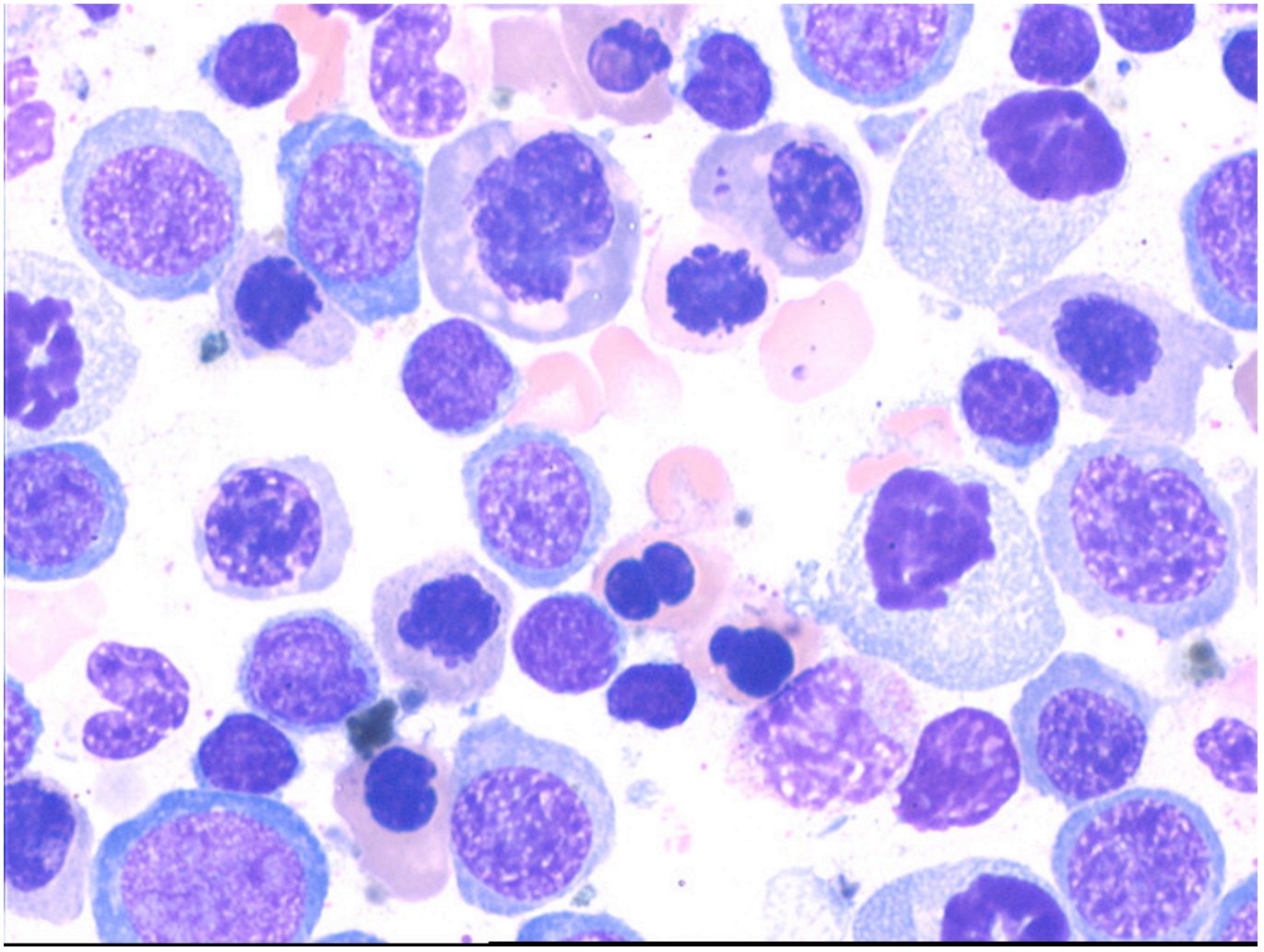


SDS-PAGE (left) and Tomato-Lectin-Binding in cda II (252/01/02/03) and normal control

Band 3



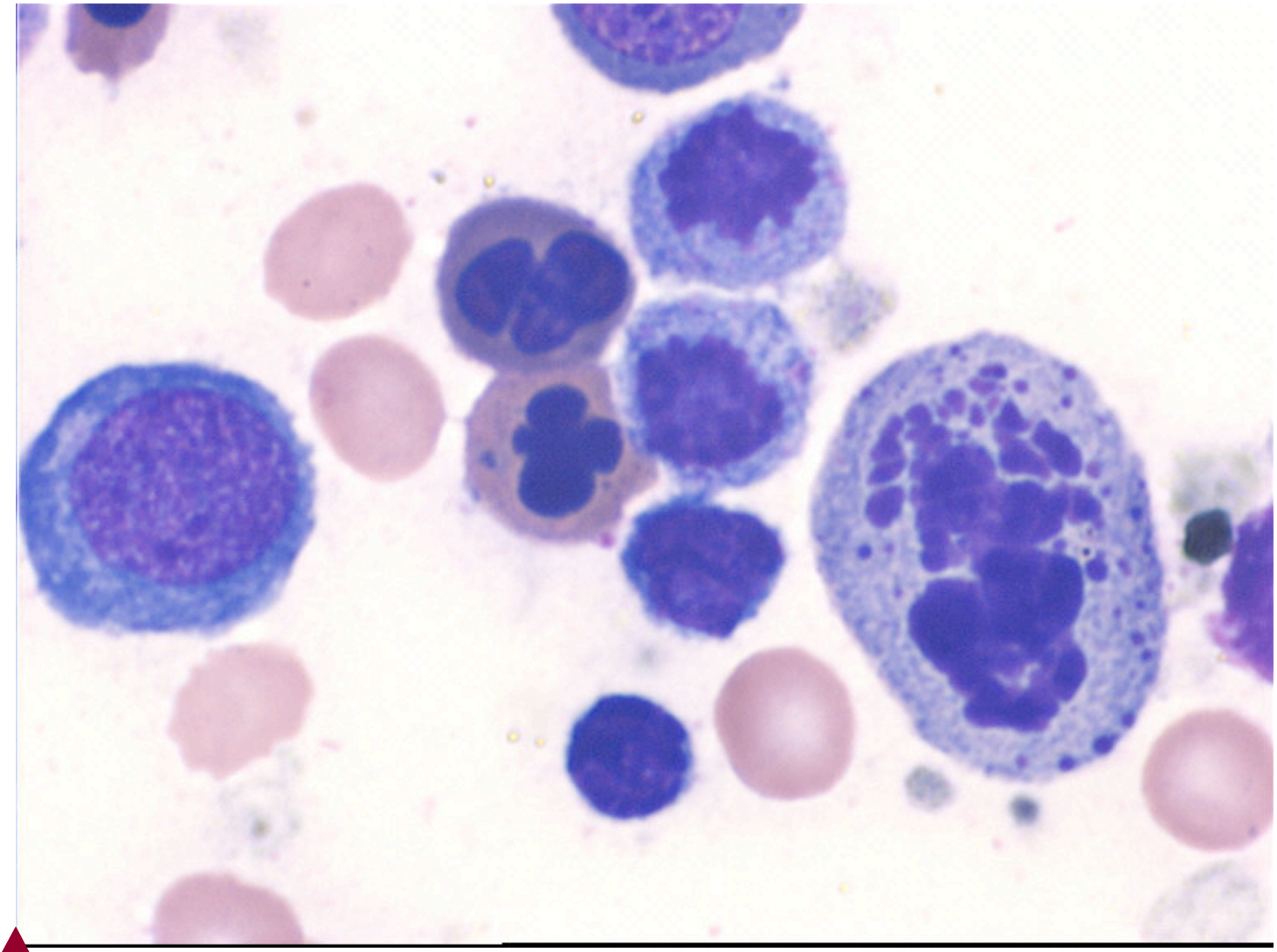
A variant of CDA: Bone marrow aspirate



2012

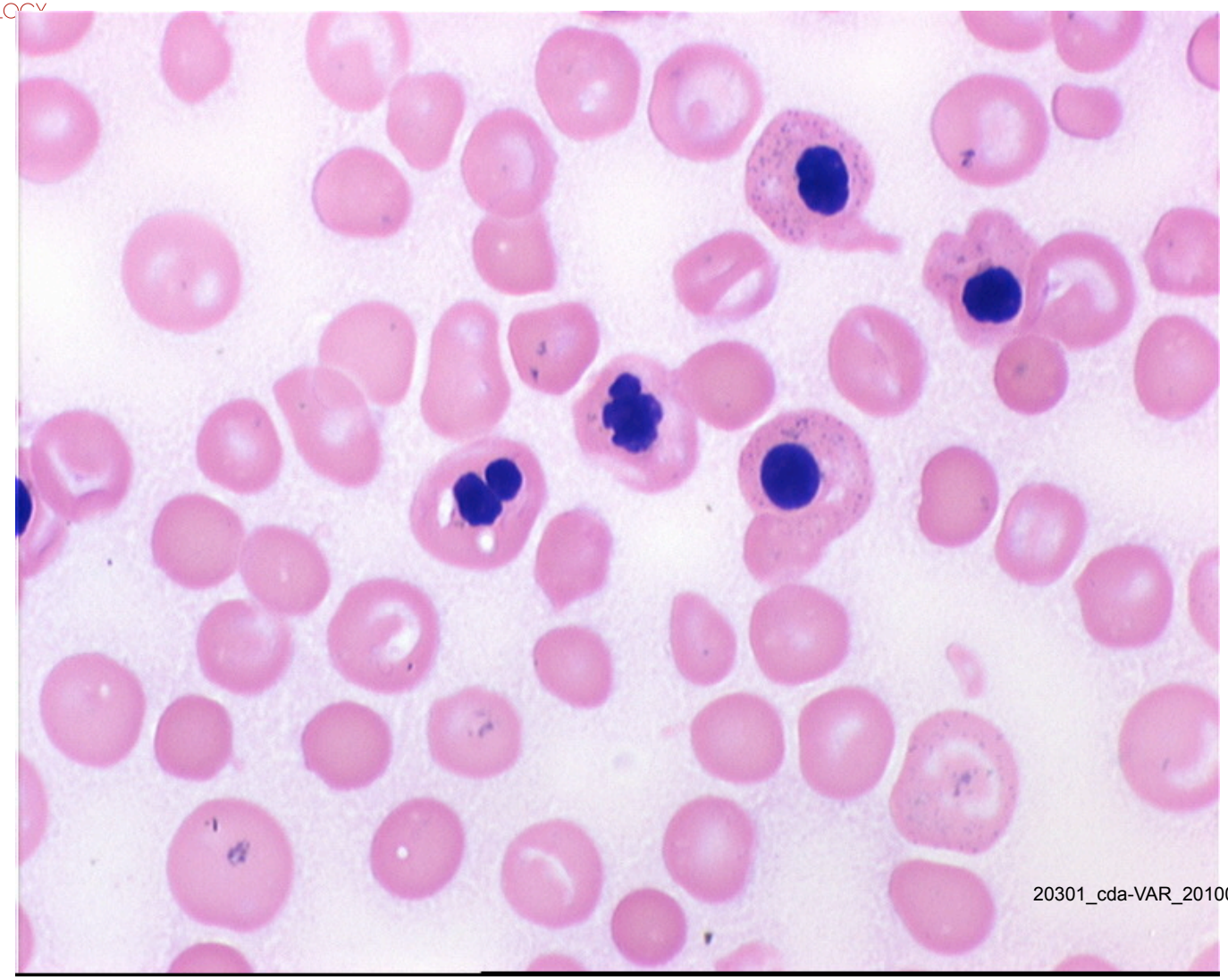
48401_140502_003.jpg

A variant of CDA: Bone marrow aspirate



48401_140502_00
5.jpg

CDA Variant, GATA-I mutation. pb after splenectomy



20301_cda-VAR_20100419_007.jpg

Highly significant differences for these

CDA I vs. controls, means in % of all erythroblasts)

- binucleated cells

  mean 5,75 (CI 4.7- 6.8) vs. 1.06 (0.3-1.8)

- abnormalities of chromatin structure

  8.8 (6.9- 10.8) vs. 0.2 (0.01- 0.4)

- chromatin bridges between erythroblasts

  3.6 (2.71- 4.4) vs. 0.14 (0.1 – 0.3)

- uncompletely divided cells

  2.8 (2.1- 3.4) vs. 0.6 (0.2- 1.0)

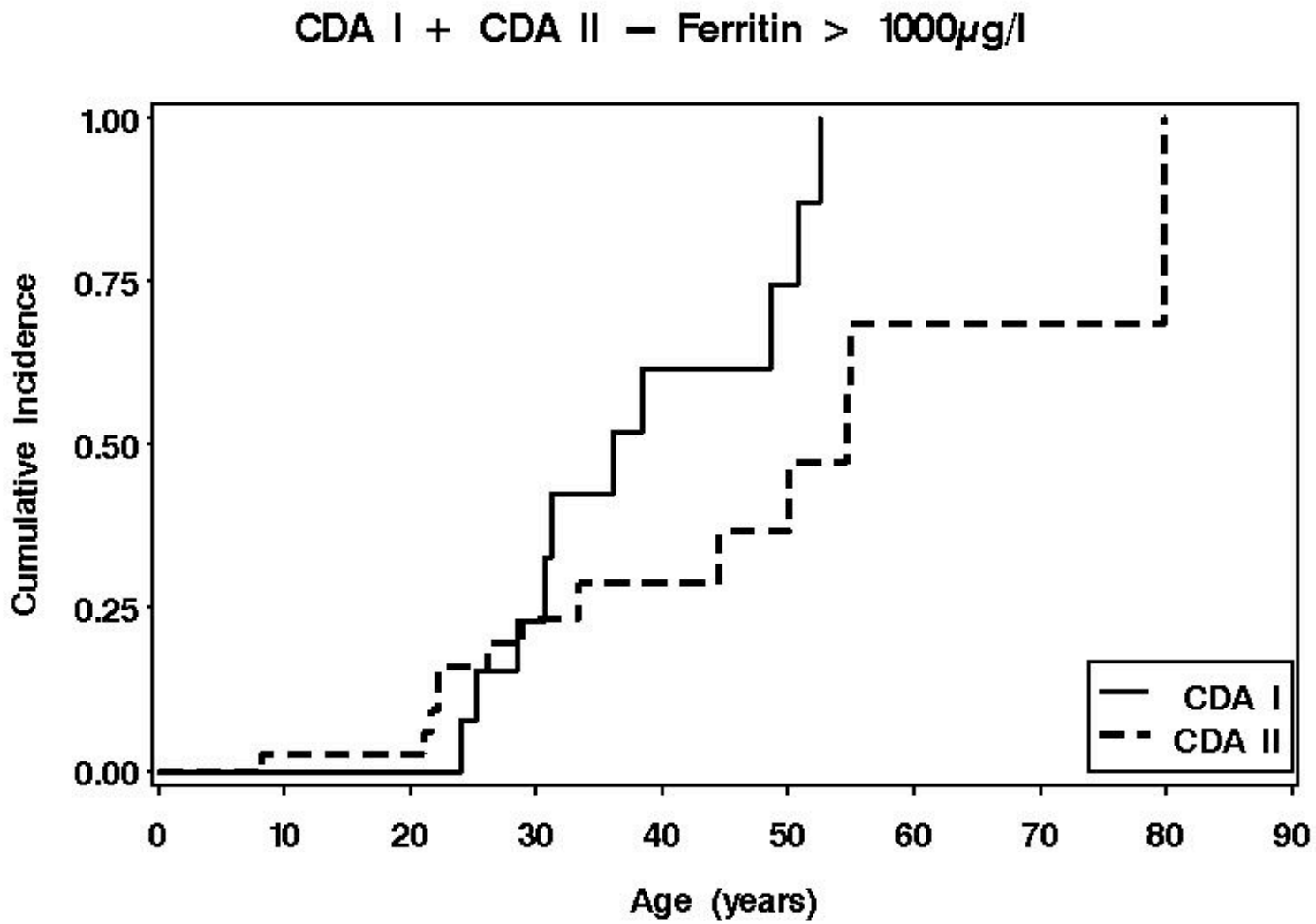
- large polyploid cells

Mann-Whitney- test with $p < 0.0001$

CDA: consequences and complications

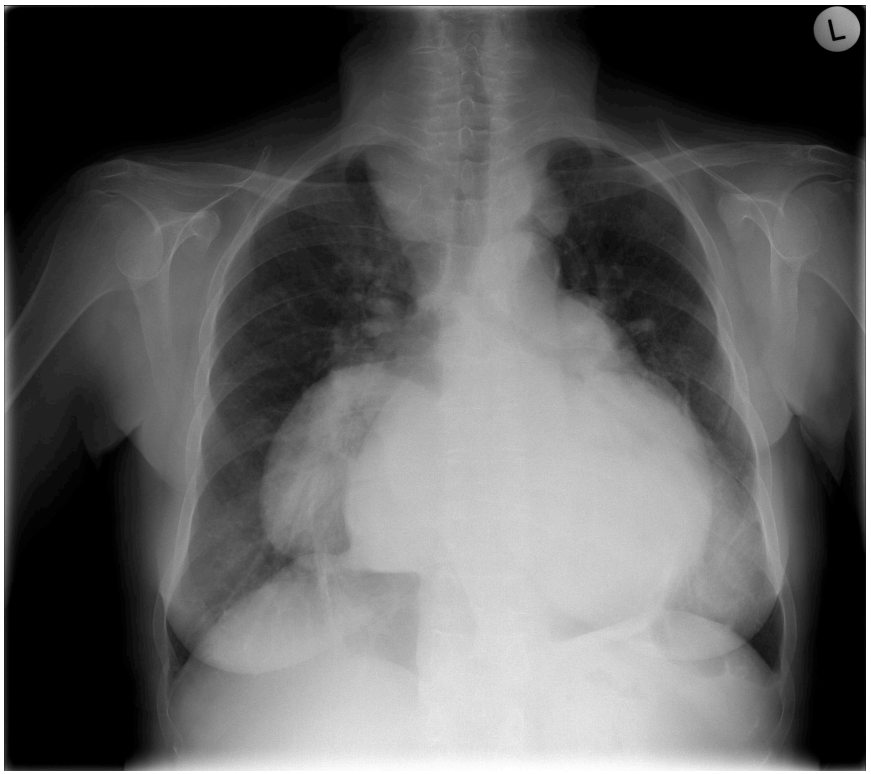
- Splenomegaly > 90%
- Iron overload, if not timely treated > 80%
- Gall stones: >70%
- Severe anemia, regular transfusions ~ 10 %
- Skeleton abnormalities by marrow expansion ~10 %
- Skeleton malformations ~10 %
- Aplastic crisis: < 10%
- Leg ulcers: < 10%
- Bulky extramedullary erythropoiesis < 5%
- Hydrops fetalis < 5%

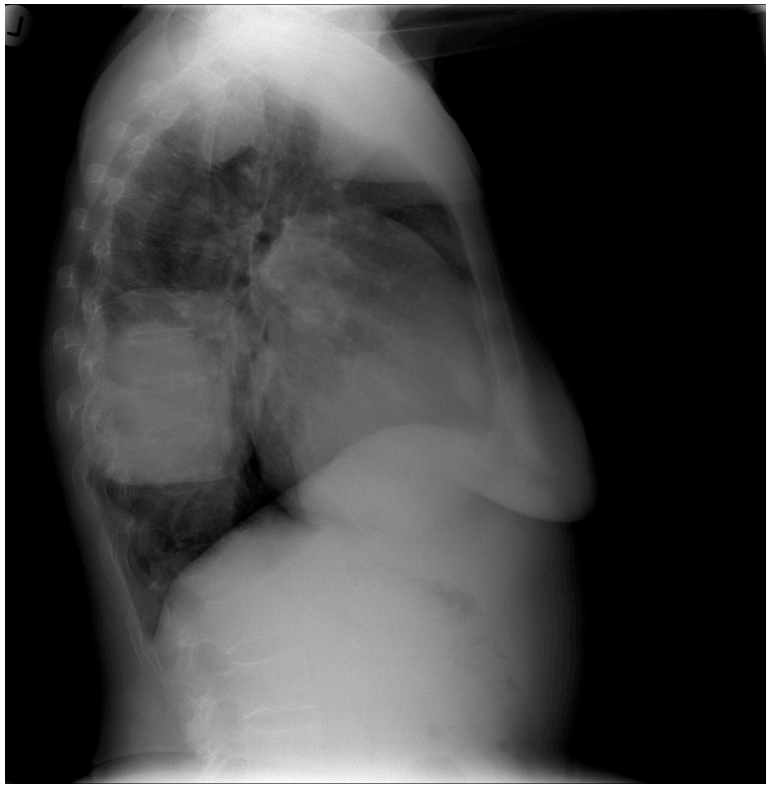
Iron overloading in CDA I and II



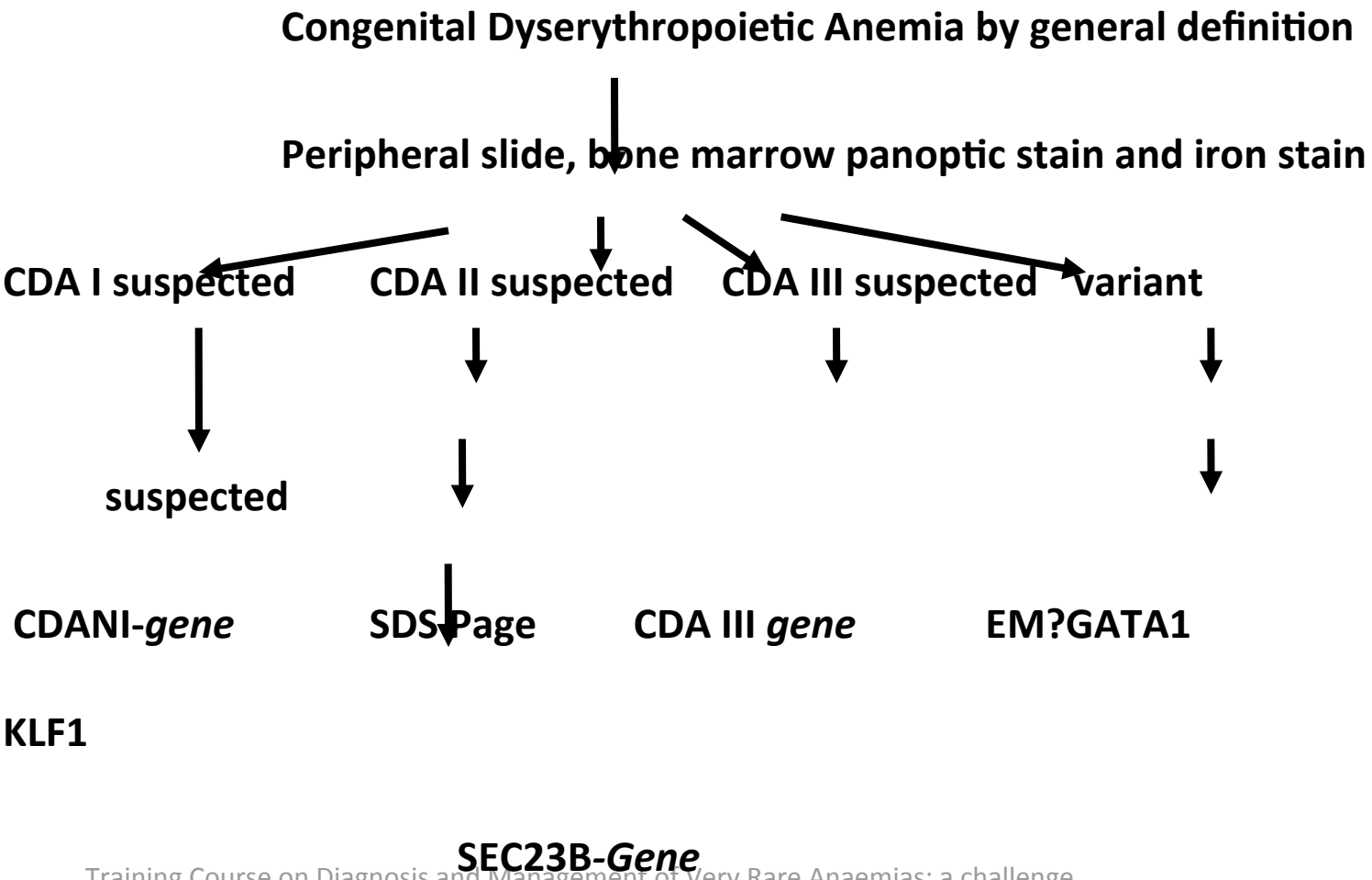
66 year old female with CDA II, 17 years after thoracotomy.

Radiographic changes were first noted at the age of 46 years





CDA: Diagnostic flow sheet



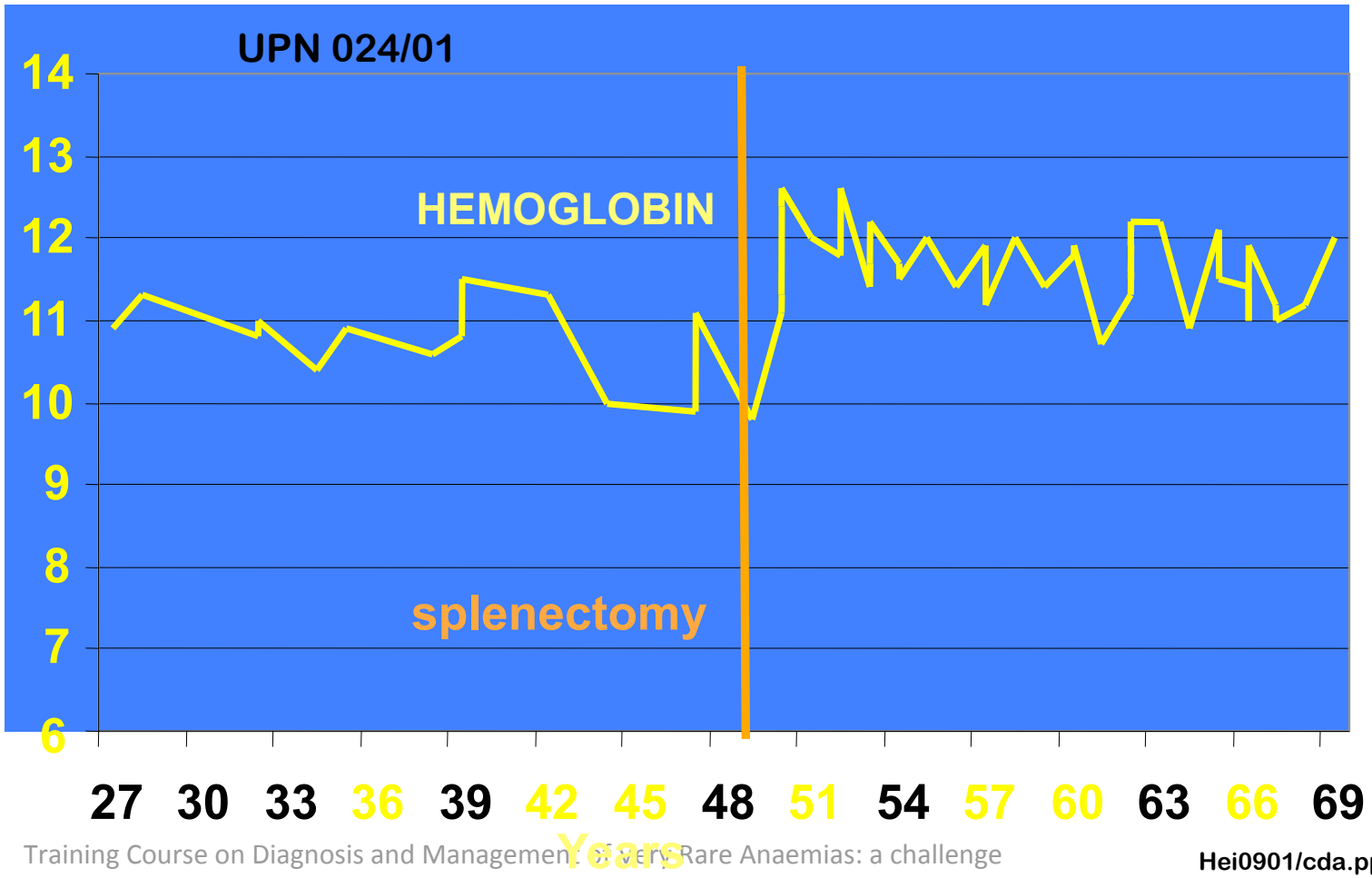
CDA: different grades of severity and therapy

- **1. Severe:** Regular transfusions needed: Type II ~ 5%
  Type I
  ~10% Tx: Type I Interferon-alpha
  Type II splenectomy
- Others Allogenic stem cell transplantation
  All types Iron chelation according to thalassemia protocols

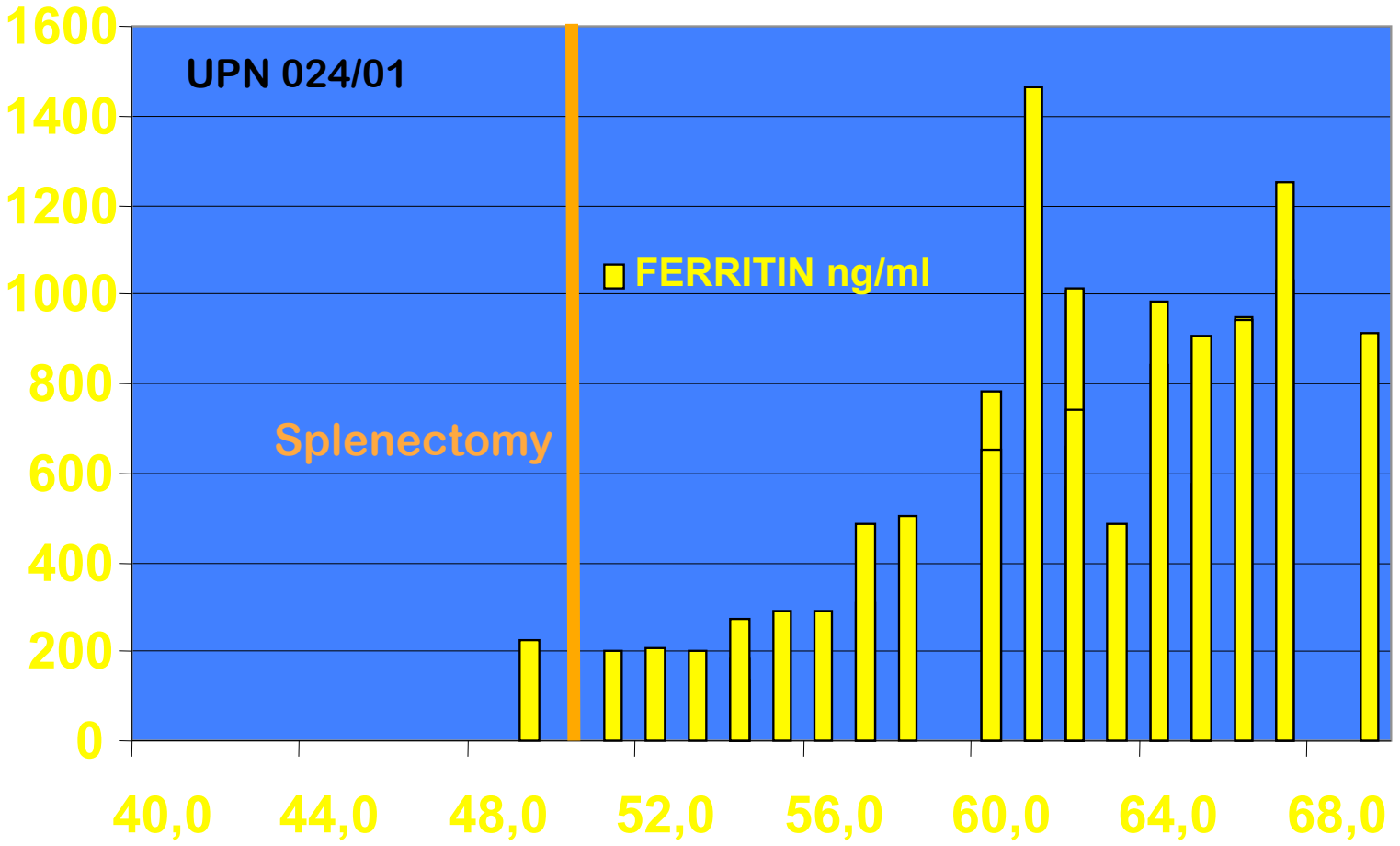
- **2. Medium:** Regular Transfusions in infancy and early childhood, but not thereafter
  Tx: Type I Interferon-alpha
  Type II Selective splenectomy
  All types Phlebotomy or iron chelation if needed

- **3. Mild:** No regular transfusions, Hb > 10 g/dl
  TX: Type I Interferon-alpha
  All types: Phlebotomy or iron chelation if needed

Congenital dyserythropoietic anemia Type II
Response of splenectomy: Hemoglobin



Congenital dyserythropoietic anemia Type II
Response of splenectomy: Serum ferritin



German Registry on CDAs, ENERCA WP6: Coworkers and Cooperations

- Ulm:

- Elisabeth Kohne (Pediatrics)
- K. Schwartz, Katja Heinrich, Tatjana Kersten (Molecular genetics)
- Rosi Leichtle (Documentation)
- Helga Dietrich (Serology)
- A.Högell (Biostatistics)
- MD Students:
- Kerstin Gallmeyer, Kerstin Kellermann, Nadine Neuschwander, Andreas Matuschek, Judith Wissmann, Christina Hepperle

- Other centers:

- J.Denecke , Muenster
- J.Goede, Zuerich
- S. Wickramasinghe +, London
- A.Iolascon, Napoli
- P.Bianchi, Milano
- J.Delaunay, Brigitte Bader – Meunier.Paris
- Florinda Gilsanz, Madrid
- L. Chroback, Prague
- Gabriela Smolenska, Jerzy. Koszielak, Eva Zdebska (+), Warzawa
- MJ King, Bristol

And many patiens, parents and physicians providing data

H. Heimpel: Disclosure of interests

- Clinical and laboratory research: Else Kröner Stiftung
- European Cooperation: ENERCA
- Lectures: Travel support from stakeholders

DGHO

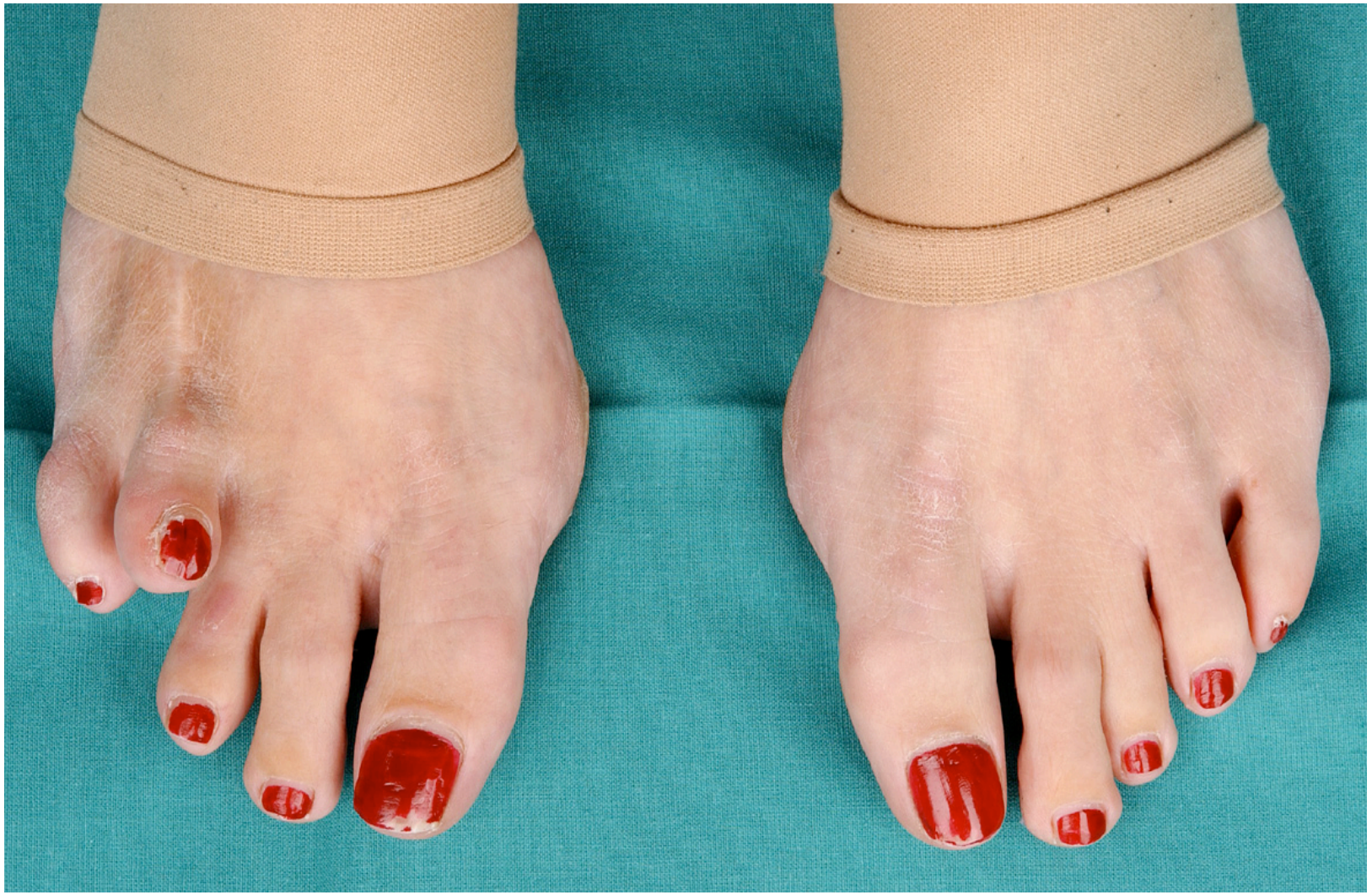
Deutsches Register für Congenitale Dyserythropoietische Anämien (CDA)

Hermann Heimpel, Elisabeth Kohne, Hubert Schrezenmeier Ulm

German Registry of Congenital Dyserythropoietic Anemia (CDA)

European Network on Rare Congenital Anemias: ENERCA

Dysostosis and Syndactyly in CDA I
Mutation in Exon 24,26



Highly significant differences for these morphological aberrations:

CDA II vs. controls means in % of all erythroblasts

- mature binucleated cells

  11.7 (CI 10,42 - 12,93) vs. 1.3 (0,4- 2.3)

- multinucleated cells

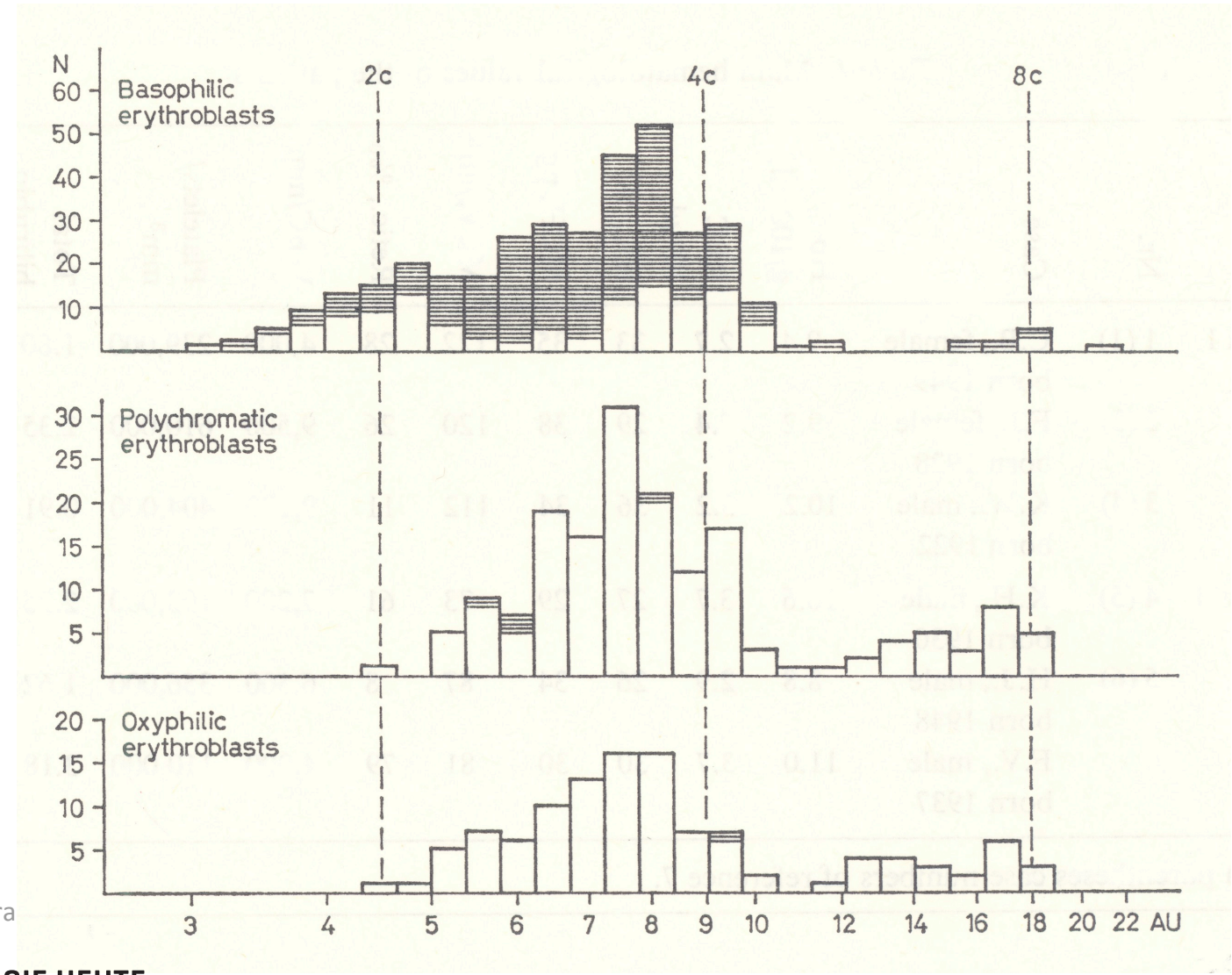
  1.1 (0.8 – 1.5) vs. 0,04 (0.01- 0.09)

Mann-Whitney- test with $p < 0.0001$

DNA –content and

H3_thymidine uptake (hatched) in a case of CDA I

Queisser at . Al, Acta haematologica 1971, 45. 65 -76



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